REMARKS

Applicant respectfully requests reconsideration. Claims 3, 4, 8-13, 39, 44, 143, 144, 147 and 149 are pending for examination with claims 3, 13, 39 and 44 being independent claims. Claims 3, 13, 39 and 149 were amended to add the limitation that the MHC class II HLA-DR ligand is an MHC class II HLA-DR binding peptide. Support for the amendment is found in the specification on page 25 lines 13-16. Claim 8 was amended to add the term "or fragment thereof". Support for the limitation is found in the specification on pages 51-54. Claim 9 was canceled. No claims have been added herewith. No new matter has been added.

Summary of Interview with Examiner

Applicant's representative wishes to thank Examiner VanderVegt for his courtesy extended during the personal interview conducted with Applicant's representative Helen Lockhart on July 19, 2006. The outstanding rejections under 35 U.S.C. § 112 were discussed. Although agreement was not reached the Examiner clarified the rejection and Applicant's representative clarified the prior response to office action. It was agreed that the rejection is not based on safety issues, i.e, concerns with systemic effects of non-target cells being activated. Rather the rejection is based on the issue of whether the "second step of the method can effectively deliver the ligand agent to the target cells." (Interview summary record). Applicant's representative indicated that arguments would be presented in the written response addressing the issue of delivering the MHC class II ligand to target cells.

Rejections under 35 U.S.C. § 112

The rejection of claims 3, 4, 8-13, 39, 44, 143, 144, 147 and 149 has been maintained under 35 U.S.C. § 112, first paragraph.

According to the Office Action dated February 9, 2006 the lack of enablement rejection is based upon the fact that the invention as claimed cannot target the specific cells to which the agent is supposed to be directed." (Page 3)

Applicant was confused by the rejection because the office action stated that "based upon the level of knowledge of the artisan, the artisan would expect that every HLA-DR molecule on every antigen-presenting cell in that subject's body was equally capable of up-regulating expression

of HLA-DR and capturing said ligand. Capture would not be limited to cancer cells." Applicant interpreted this statement to mean that there was a worry of non-specific interactions with the ligand leading to side effects and safety issues. However, it was clarified during the interview and in the Interview Summary Form that the rejection is based on the issue of whether the "second step of the method can effectively deliver the ligand agent to the target cells." (Interview summary record).

As discussed in the interview, Applicant believes the specification provides an enabling disclosure of methods for delivering the MHC class II ligand to target cells. Applicant has amended the claims to clarify the issue by reciting that the MHC class II ligand is an MHC class II HLA-DR binding peptide. The specification teaches one of skill in the art how to deliver and formulate MHC class II HLA-DR binding peptides such that they reach and affect the target cells. In the specification on page 25 it is taught that "these peptides can be used as a ligand in a soluble form or may be attached or conjugated to a carrier such as a liposome or particle (other chemical/physical vectors useful for this purpose are discussed below)." The specification on pages 59-62 describe examples of chemical/physical vectors that can be used to deliver the peptides to target cells. For instance, on page 60, it is taught that :

> "Liposomes may be targeted to a particular tissue, such as the site of a tumor, by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein. Ligands which may be useful for targeting a liposome to a tumor cell include, but are not limited to: intact or fragments of IRM which interact with tumor cell specific receptor and molecules which interact with the cell surface markers of tumor cells such as antibodies. Such ligands may easily be identified by binding assays well known to those of skill in the art."

The specification on page 48 line 31 to page 49 line 1 teaches that methods for making and identifying binding peptides which bind to a particular target are well known in the art. The pages that follow describe examples for carrying out the known methods.

On page 69 of the specification, Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton PA) is cited for it's teaching with respect to carriers and formulations for different types

administration. The text of the Remington's is incorporated by reference (page 97 of the specification).

Chapter 61 of Remington's, 18th edition, 1990, is directed to antineoplastic and immunoactive drugs. The text describes well know methods for delivering drugs to tumors. For instance it is taught on page 748 (chapter 37) that

> "Close intra-arterial administration of drugs is used to get drugs directly to a target site or organ in high concentrations. After it has passed through the target region it is distributed in the entire blood volume, which reduces the systemic levels of the drug and the consequent side effects. One example is the use of cytotoxic drugs for the treatment of primary or metastatic tumors of the liver. The infusion of drugs in to the hepatic artery exposes the tumor to higher drug concentrations than can be tolerated with intravenous administration. If the drug is extracted efficiently by the liver, the exposure of sensitive tissues such as bone marrow and gastrointestinal epithelium to the drug will be decreased. For example, after hepatic artery infusion of floxuridine (FUDR), hepatic vein concentrations are 2 to 6 times higher than comparable drug concentrations following intravenous infusion, yet systemic blood concentrations are 75% less. Thus, the therapeutic index of FUDR in the treatment of liver cancer is increased considerably by hepatic arterial infusion. This type of selective drug administration may be beneficial with other drugs that have low therapeutic indices."

The above-cited paragraph describes techniques that were well known at the time of the invention. The publication is from 1990, several years before the priority date of the instant application and is found within a well respected textbook in the art of pharmacology. Using such knowledge in combination with the detailed teachings found in the specification, one of skill in the art would have been able to administer the binding peptides to a subject to produce the claimed result.

Additionally, the binding peptides may be antibodies or antibody fragments (e.g. claim 8). As shown in Chapter 74 of Remington's on pages 1427-1428 (copy enclosed as Exhibit 1), 17 antibodies were in various stages of clinical trials for the treatment of cancer in 1990. Those of skill in the art knew how to administer antibodies to target different types of tumor cells at the time of the invention.

Furthermore, Chapter 91 of Remington's , pages 1691-1693 (copy enclosed as Exhibit 2) describe target delivery systems, similar to the description found in Applicant's specification,

including a discussion of nanoparticles and liposomes as targeted delivery systems. On page 1693 the section on Immunologically Based Systems provides a discussion of targeting drugs to specific tissues, such as tumor tissue.

The above descriptions in the specification, combined with what was known in the art at the time of the invention was adequate to demonstrate to one of skill in the art at the time of the invention that administering a binding peptide using the methods described in the specification would result in the engagement of the HLA-DR molecule with the binding peptide in a manner sufficient to decrease mitochondrial membrane potential in the cell.

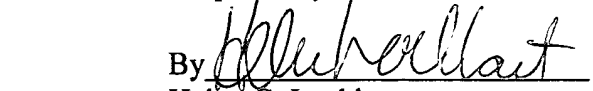
In view of the teaching of the instant application and the state of the art at the time of filing, Applicant submits that the claimed invention can be practiced without undue experimentation. Applicant has provided compounds that induce HLA-DR and compounds that are ligands thereof and have provided guidance to one of ordinary skill in the art to use these compounds to decrease mitochondrial membrane potential. Modes of delivery and targeting are well known in the art. Therefore, the amount of experimentation required to practice the invention is not undue. One of ordinary skill in the art would be able to administer the claimed compounds of the invention using no more than routine experimentation with Applicant's disclosure in hand.

Accordingly, withdrawal of the rejection of claims 3, 4, 8-13, 39, 44, 143, 144, 147 and 149 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: August 9, 2006

Respectfully submitted,

By 

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Appendix A—Continued

Interferon-gamma	Genentech* (San Francisco CA)	cancers (small-cell lung, melanoma, colorectal)	Phase III
Interferon-gamma	Interferon Sciences (New Brunswick NJ)	scleroderma	Phase I
Interferon-consensus	Amgen** (Thousand Oaks CA)	cancer, infectious disease	Phase II/III
		Interleukins	
Interleukin-2	Amgen** (Thousand Oaks CA) Johnson & Johnson* (New Brunswick NJ)	cancer immunotherapy	Phase II
Bioleukin Interleukin-2	Biogen** (Cambridge MA) Glaxo* (Research Triangle Park NC)	cancer immunotherapy	Phase I
PEG† Interleukin-2	Cetus** (Emeryville CA)	cancer	Phase I
Proleukin Interleukin-2	Cetus** (Emeryville CA)	cancer	Phase III
Interleukin-2	Collaborative Research (Bedford MA)	cancer immunotherapy	Phase I
Recombinant Human Interleukin-2	Hoffmann-La Roche* (Nutley NJ) Immunex (Seattle WA)	cancer immunotherapy	in clinical trials
Recombinant Human Interleukin-2/LAK Cell Therapy	Hoffmann-La Roche* (Nutley NJ)	cancer immunotherapy	in clinical trials
Recombinant Human Interleukin-2/Roferon-A Combination	Hoffmann-La Roche* (Nutley NJ)	cancer immunotherapy	in clinical trials
		Monoclonal Antibodies	
Anti-Leu-2† MAb	Becton-Dickinson (Mountain View CA)	renal-allograft rejection	Phase I
		prevention of graft vs host disease	Phase II
MAb-L6	Bristol-Myers/Oncogen* (New York NY)	lung cancer	Phase I
Centoxin MAb	Centocor (Malvern PA)	septic shock	Phase III
Panorex MAb	Centocor (Malvern PA)	colorectal cancer, pancreatic cancer	Phase II
Ovarian RT MAb	Centocor (Malvern PA)	ovarian cancer	Phase I
Centorex Anti-platelet MAb	Centocor (Malvern PA)	anti-platelet prevention of blood clots	Phase I
MAb	Cetus** (Emeryville CA)	breast cancer	Phase I
OncoRad† MAb	CYTOGEN Corp. (Princeton NJ)	ovarian cancer	Phase I
OncoScint CR103† MAb	CYTOGEN Corp (Princeton NJ)	colorectal cancer	Phase III
OncoScint OV103† MAb	CYTOGEN Corp. (Princeton NJ)	ovarian cancer	Phase II/III
KS 1/4-DAVLB MAb	Eli Lilly* (Indianapolis IN)	cancer	in clinical trials

Appendix A—Continued

ADDC agent MAb	Genetics Institute** (Cambridge MA) NeoRx (Seattle WA)	colorectal cancer	Phase I
Anti-IL-2 Receptor MAb	Immunex (Seattle WA) Becton-Dickinson (Mountain View CA)	prevention of graft-host disease in bone marrow transplants	Phase II
MAb	Immunomedics (Newark NJ) Johnson & Johnson* (New Brunswick NJ)	colorectal cancer	Phase II
MAb	Lederle* (Wayne NJ)	cancer	in clinical trials
Colorectal, Rhenium-186† MAb	NeoRx (Seattle WA)	colorectal cancer	Phase I
Melanoma I-131 MAb	NeoRx (Seattle WA)	malignant melanoma	Phase I
Ovarian I-131 MAb	NeoRx (Seattle WA)	ovarian cancer	Phase I
Ovarian, Pseudomonus Exotoxin† MAb	NeoRx (Seattle WA)	ovarian cancer	Phase I
ORTHOCLONE OKT3 MAb	Ortho Pharmaceutical* (Raritan NJ)	heart and liver transplant rejection	application submitted
Xomen-E5 MAb	Pfizer* (New York NY) Xoma (Berkeley CA)	septic shock	Phase III
XomaZyme-Mel MAb	Xoma (Berkeley CA)	melanoma	Phase II
XomaZyme-791 MAb	Xoma (Berkeley CA)	colorectal cancer	Phase II
XomaZyme-H65 MAb	Xoma (Berkeley CA)	bone marrow rejection, transplant graft vs host disease	Phase III
		rheumatoid arthritis	Phase I
	Peptides		
Auriculin Atrial Peptide (injectable)	California Biotechnology (Mountain View CA) Wyeth-Ayerst* (Philadelphia PA)	acute congestive heart failure	Phase II
Pentigetide† (aerosol)	Immunetech** (San Diego CA)	asthma	Phase I
Pentigetide (injectable)		allergic rhinitis	application submitted
Pentigetide (nasal spray)		allergic rhinitis	application submitted
Pentigetide (ophthalmic)		allergic conjunctivitis	Phase III
TCMP-80 T-cell Modulatory Peptide	Immunetech** (San Diego CA)	auto-immune diseases	Phase I
Brady kinin antagonists† (nasal spray)	Nova Pharmaceutical** (Baltimore MD) SmithKline Beckman* (Philadelphia PA)	common cold	Phase II

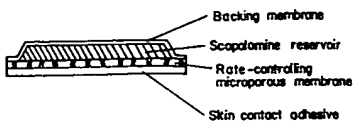

Fig 91-16. Schematic diagram of a transdermal device for delivery of scopolamine.

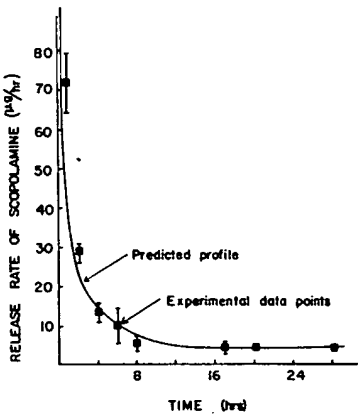

Fig 91-17. *In-vitro* release rate versus time profile for scopolamine from a transdermal device. (Reproduced with permission.[12])

the membrane are filled with a fluid which is highly permeable to scopolamine. An initial priming dose of drug is contained in a gel on the membrane side of the device. The delivery rate is governed by diffusion through the various lamellae of the device and the skin. At a steady state, the rate-limiting step is diffusion across the microporous membrane. One particular model of the device is 200 μm thick, covers a skin surface area of 2.5 cm^2 and is designed to release 500 μg of scopolamine at an approximately constant rate for a period of 3 days. It generally is applied behind the ear. A typical *in vitro* release rate versus time profile from such a system is shown in Fig 91-17.

More recently, transdermal systems have been developed for delivery of nitroglycerin. Nitroglycerin is indicated for treatment of pain caused by angina pectoris. Sublingual dosage forms of nitroglycerin were the first type available for antianginal use, but they suffer from a short duration of action due to rapid metabolism in the liver and other organs by the enzyme glutathione-organic nitrate reductase. This short duration of action is acceptable for treating acute anginal attacks, but it is unfavorable when a prophylactic effect is desired. Orally administered nitroglycerin is metabolized extensively during its first pass through the liver, and it is debatable whether sufficient amounts of the drug reach the systemic circulation to elicit the desired response. Topical ointments were developed in an attempt to extend the duration of action, but only a 4- to 8-hour effect is achieved and patient compliance is a problem. The fourth generation in nitroglycerin delivery systems is the transdermal device, which offers a significant improvement in sustained-release therapy over its predecessors. There are three different products in several sizes currently on the market that release from 2.5 to 22.4 mg over 24 hours, depending on the drug content and surface area covered. One of the products, Transderm-Nitro (*Ciba*), uses a microporous membrane similar to that used in the scopolamine device as the rate-controlling barrier. The Nitrodisc (*Searle*) uses drug microsealed in a solid silicone polymer, and the Nitro-Dur (*Key*) uses a 2% diffusion matrix. The devices range from 5 to 20 cm^2 in surface area and generally are applied to the upper arm or chest.

Targeted Delivery Systems

Nanoparticles

Nanoparticles are one of several types of systems known collectively as colloidal drug delivery systems. Also included in this group are microcapsules, nanocapsules, macromolecular complexes, polymeric beads, microspheres and liposomes. A nanoparticle is a particle containing dispersed drug with a diameter of 200 to 500 nm. The size of a nanoparticle allows it to be administered intravenously via injection, unlike many other colloidal systems which occlude both needles and capillaries. Materials used in the preparation of nanoparticles are sterilizable, nontoxic and biodegradable; examples are albumin, ethylcellulose, casein and gelatin. They usually are prepared by a process similar to the coacervation method of microencapsulation.

There have been two main applications of nanoparticles: as carriers of medical diagnostic agents such as radioisotopic technetium-99m and fluorescein isothiocyanate, and for the delivery of liver flukicides in veterinary medicine. Radioisotopes are used to study the morphology, physiology and blood flow of various organs in the body. The liver commonly is visualized with a technetium-99m/sulfur colloid. Preparation of technetium-99m gelatin nanoparticles, and subsequent intravenous injection into mice, revealed that they are taken up rapidly by the reticuloendothelial system and localized mainly in the liver.[24] The reticuloendothelial system consists of phagocytic cells designed to cleanse the bloodstream of bacteria, viruses, cell debris and other unwanted foreign particles. The behavior of nanoparticles *in vivo* is the same as that exhibited by other colloidal systems of similar size, and points to the possibility of using nanoparticles to target drugs to the liver and phagocytic cells. The use of fluorescein isothiocyanate (FITC) was aimed at determining the availability of surface amino groups on gelatin or albumin nanoparticles. Since FITC is known to bind to amino groups, any such binding on the surface of a nanoparticle would reveal the presence of amino groups and thus their possible use as binding sites for drug molecules as well. Results indicated that free amino groups are, indeed, present on the surface of the nanoparticle.[24] In addition, preliminary work showed that FITC gelatin nanoparticles incubated with tumor cells *in vitro* are taken up by the tumor cells. This observation suggests the possible use of nanoparticles for the targeted delivery of anticancer agents to tumorous tissue.

Liposomes

When phospholipids are dispersed gently in an aqueous medium, they swell, hydrate and spontaneously form multilamellar concentric bilayer vesicles with layers of aqueous media separating the lipid bilayers. These systems commonly are referred to as multilamellar liposomes or multilamellar vesicles (MLVs) and have diameters of from 25 nm to 4 μm. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core. Liposomes bear many resemblances to cellular membranes and have been used for over a decade to study membrane behavior and membrane-mediated processes. It also is possible to use liposomes as carriers for drugs and macromolecules since water- or lipid-soluble substances can be entrapped in the aqueous spaces or within the bilayer itself,

respectively. More-recent studies have been aimed at investigating the potential of these drug-bearing liposomes for site-specific or receptor release of their active agent.

Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. Physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. They show low permeability to ionic and polar substances, including many drugs, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars or drugs. In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins such as cytochrome-C bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly; most liposome formulations used for drug delivery contain cholesterol to help form a more closely packed bilayer system during preparation. Serum high-density lipoproteins cause significant leakage in the membrane, probably due to removal of phospholipid.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs. In addition to liposome characteristics, an important determinant in drug entrapment is the physicochemical properties of the drug itself. As mentioned previously, polar drugs are trapped in the aqueous spaces and nonpolar drugs bind to the lipid bilayer of the vesicle. Polar drugs are released when the bilayer is broken, or by permeation but, nonpolar drugs remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes can interact with cells by four different mechanisms:[25]

1. Endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils.
2. Adsorption to the cell surface either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components.
3. Fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm.
4. Transfer of liposomal lipids to cellular or subcellular membranes, or *vice versa*, without any association of the liposome contents.

It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity and surface charge. They may persist in tissues for hours or days, depending on their composition, and half-lives in the blood range from minutes to several hours. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but the physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow and lymphoid organs.

Attempts to overcome the limitation on targeting of liposomes have centered around two approaches. One is the use of antibodies, bound to the liposome surface, to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. A second approach is to use carbohydrate determinants as recognition sites. Carbohydrate determinants are glycoprotein or glycolipid cell-surface components that play a role in cell–cell recognition, interaction and adhesion. Although the precise mechanism of their action is still unknown, they show potential in directing liposomes to particular cell types by their inclusion in the liposomal membrane. A discussion of the factors influencing targeting of liposomes has been given by Gregoriadis *et al.*[26] Potential therapeutic applications of liposomes include their use in the treatment of malignant tumors, lysosomal storage diseases, intracellular parasites, metal toxicity and diabetes. The liposome acts as the carrier of the active agent used in treatment of these conditions. Most of the applications involve intravenous injection of the liposomal preparation, but other routes of administration are conceivable. For example, liposome-entrapped insulin may offer some degree of protection of drug from gastric degradation and the possibility of GI absorption by endocytosis. Further details of current applications of liposome-entrapped drugs can be found in the literature.[25,26]

Resealed Erythrocytes

When erythrocytes are suspended in a hypotonic medium, they swell to about one and a half times their normal size, and the membrane ruptures resulting in the formation of pores with diameters of 200 to 500 Å. The pores allow equilibration of the intracellular and extracellular solutions. If the ionic strength of the medium then is adjusted to isotonicity and the cells are incubated at 37°, the pores will close and cause the erythrocyte to "reseal." Using this technique with a drug present in the extracellular solution, it is possible to entrap up to 40% of the drug inside the resealed erythrocyte and to use this system for targeted delivery via intravenous injection. The advantages of using resealed erythrocytes as drug carriers are that they are biodegradable and nonimmunogenic, exhibit flexibility in circulation time depending on their physicochemical properties, the entrapped drug is shielded from immunologic detection and chemical modification of drug is not required.

The assessment of resealed erythrocytes for use in targeted delivery has been facilitated by studies on the behavior of normal and modified reinfused erythrocytes. In general, normal aging erythrocytes, slightly damaged erythrocytes and those coated lightly with antibodies are sequestered in the spleen after intravenous reinfusion, but heavily damaged or modified erythrocytes are removed from the circulation by the liver.[27] This suggests that resealed erythrocytes can be targeted selectively to either the liver or spleen, depending on their membrane characteristics. In addition to coating with antibodies, removal of portions of cell-surface carbohydrates reduces the circulating half-life.

The ability of resealed erythrocytes to deliver drug to the liver or spleen can be viewed as a disadvantage in that other organs and tissues are inaccessible. Thus, the application of this system to targeted delivery has been limited mainly to treatment of lysosomal storage diseases and metal toxicity, where the site of drug action is in the reticuloendothelial

system. A more detailed discussion of the application of resealed erythrocytes has been presented by Ihler.[28]

Immunologically Based Systems

As discussed in the section pertaining to intramuscular injections, the formation of dissociable complex of a drug with a macromolecule is a viable method of achieving a sustained-release effect. If the macromolecule used is an antibody, an antigen-specific targeted effect also can be achieved. In addition to complex formation by noncovalent forces, drugs also may be linked covalently to antibodies, provided the activity of both drug and antibody is retained or the activity of drug is recoverable after release.

Most studies of antibody–drug systems have employed covalent conjugation of the drug to the antibody. Chemical crosslinking agents are used commonly to attach a drug to an antibody by reacting with appropriate groups available on both species. Among the crosslinking agents used are carbodiimide, glutaraldehyde, bisazobenzidine, cyanuric chloride, diethylmalonimidate or various mixed anhydrides. The reaction should allow effective control of the antibody–drug conjugate size, and the crosslink must readily be broken by available lysosomal hydrolases within the receptor cell, if drug release is critical to activity.

Certain specificities expressed on tumor cells, referred to as membrane-bound tumor-associated antigens (TAAs), may be exploited for the purpose of targeting antibody–drug conjugates directly at the malignant tumor by various parenteral routes of administration. Since anticancer drugs are indiscriminate to cell type in their action, a targeted delivery system for these drugs would offer a significant improvement in cancer chemotherapy. A wide variety of antineoplastic drugs have been conjugated to tumor-specific antibodies. Three that have received the most attention are chlorambucil, adriamycin and methotrexate. The effectiveness of these systems depends on the nature of the crosslinking agent and the method of reaction. The interested reader is directed to two reviews that discuss the use of antibody–drug conjugates for treatment of tumors.[29,30]

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